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Research experiments and projects pertaining to the ocular hazards of lasers and other optical sources during the period 1962-1982 as performed in this laboratory are reviewed and discussed in some detail. Early studies to determine threshold retinal damage in the rabbit from ruby and neodymium lasers are described and followed by more elaborate experiments with monkeys using the He;Ne laser. A comparison between threshold retinal lesions in human volunteers, monkeys and rabbits is given. Retinal damage in the rhesus monkey is evaluated in terms of visual acuity. Quantitative data on solar retinitis as determined in the rhesus monkey are provided and the effects of wavelength on light toxicity are evaluated for eight monochromatic laser lines. Experiments performed at Los Alamos to evaluate the ocular effects and hazards of picosecond and nanosecond pulses of radiation from CO_2 and HF lasers are described. A list of published papers decribing the above research is included.

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FOREWORD

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William T. Hamm, Jr. 2/19/88

PI Signature Date

3. INTRODUCTION (BACKGROUND):
Research on the ocular effects of radiation began in this laboratory in 1956 when we were solicited by the Armed Forces Special Weapons Project (AFSWP) to investigate ocular hazards from the nuclear fireball. Rabbits exposed in Nevada to a nuclear fireball had received retinal lesions at 42 miles from the detonation.[1] Our research program began as an Air Force project but was also financed by the Defense Atomic Support Agency (DASA) which had replaced AFSWP in the Pentagon.

Under Army contract DA-49-007-MD-99 with the Surgeon General's Office we had already developed an apparatus to simulate flash burns from the nuclear fireball.[2] The source consisted of a 24 inch Army searchlight with a high intensity carbon arc. The experimental production of flash burns in the rabbit retina was accomplished by using two ellipsoidal mirrors to focus the radiation from the carbon arc on the rabbit retina.[3] These data were evaluated by probit analysis and used to assess the hazards of flashblindness and/or retinal injury to pilots in the Strategic Air Command (SAC) and the Tactical Air Command (TAC) as well as the eye hazard for the Army, Navy and Marine Corps under nuclear tactical warfare operations. Data from this research were also useful to the Atomic Energy Commission (AEC) during the high altitude test series over Johnson Island in 1958.[4] Evaluation of the ocular hazard as a function of the yield and distance from nuclear fireballs necessitated security clearance with the Department of Defense (DOD) and the AEC. While no classified research was performed in our laboratory, access to security information was necessary. One of us (Dr. Ham) participated in the first nuclear test series within the continental United States, Operation Ranger, January 1951. Data obtained in the field during this series of detonations of small yield weapons (<20 KT) indicated that peak irradiance from the fireball occurred in less than 200 milliseconds. At the time, 1951, a report of these data to the Army was classified secret. In a second series of nuclear tests (Operation Buster-Jangle), animals transported to Nevada by the Air Force in October 1951 were exposed to the thermal flash from a nuclear airdrop. These burn data collected in the field were correlated with burn data produced in the laboratory by the high intensity carbon arc searchlight on animals and human volunteers.

The same apparatus developed to produce flash burns in the rabbit retina was used in 1957 to treat successfully a macular angioma in a patient.[5] This represented the first photocoagulation of the retina performed in this country. Subsequent investigation revealed that Meyer-Schwickerath in conjunction with the Zeiss Optical Company had developed a xenon lamp photocoagulator in Germany.[6] One of the first of these light coagulators was purchased and installed in our laboratory in 1959. In consequence, the Department of Ophthalmology at the Medical College of Virginia became a pioneer in the clinical applications of light coagulation. A research photocoagulator employing a 1600 W xenon lamp with associatd optics modeled after the

Zeiss instrument was developed to produce short pulses of less than 200 milliseconds.[7] This apparatus modified with a 2500 W lamp, quartz optics, filters, "hot" and "cold" mirrors, electronic control and timing has been developed into a sophisticated research tool capable of providing a simulated solor spectrum and 10 nm bandwidths throughout the near ultraviolet, visible and near infrared spectrum.

This early ocular research before lasers became available (1951-1960) involved short exposure times and high retinal irradiances that made it valid to assume that thermal injury was the basic mechanism involved in retinal damage. With the advent of lasers in 1959-1960, it was a natural consequence of our background to become involved in research concerning the ocular effects of lasers. This research was supported by the Office of the Surgeon-General, U.S. Army, under contract number DA-49-193-MD-2241, entitled "Biological Applications and Effects of Optical Masers", that became operational on February 1, 1962. A group of papers on the ocular effects of lasers were published under this contract which was superceded on July 1, 1972 by contract DADA17-72-C-2177.

Since its inception in 1962 this research program has provided valuable biological data leading to the establishment of ocular safety standards by the Armed Services, the American National Standards Institute (ANSI Z-136 and Z-311) and other groups including the American Industrial Hygiene Association (AIHA) and the American Conference of Governmental Industrial Hygienists (ACGIH). A primary objective was to establish safe exposure levels to the eye of laser radiation, particularly those wavelengths used by the Armed Services. Laser wavelengths investigated include the following: CO_2 10.6 micrometers, HF and DF at 2.5-3.0 micrometers, GaAs at 820, 830, 850 and 905 nm, He:Cd at 441 and 325 nm, argon-krypton at 458, 488, 514 and 647 nm, He:Ne at 633 nm, Nd:YAG at 1064 and 532 nm and argon at 351 and 363 nm. It was shown that wavelengths in the near infrared emitted by GaAs lasers (820-910 nm) do not present an ocular hazard at the levels used by the MILES prototype system or in fiber optic communication systems. By 1966 enough burn threshold data for the rabbit retina had been accumulated, including some laser data, to plot retinal irradiance in $W \cdot cm^{-2}$ vs exposure time in seconds over 10 log units of time, from 30 nanoseconds to 100 seconds.[8] Plotted logarithmically, these data fell on a straight line from 3 megawatts$\cdot cm^{-2}$ and 30 nanoseconds to 10 $W \cdot cm^{-2}$ at 1 second. For exposure durations beyond 1 second the curve flattened out asymptotically along the abscissa but never quite reached a plateau. The common interpetation was that the plateau represented a temperature too low to cause thermal denaturation. There was no evidence at that time to indicate a wavelength dependence. In fact, over the straight portion of the curve it was immaterial whether the radiation was infrared or visible, coherent or incoherent. Our research on the retinal effects of near infrared, visible and short wavelength light, sunlight and near ultraviolet radiation since that

time has improved our perspective and understanding of retinal phototoxicity. In the following sections of this progress report we shall review our findings between 1962 and 1982 that led up to the modern concept of light damage. All of these findings have been published in the scientific literature.

4. EARLY STUDIES WITH RUBY (693.4 nm) AND NEODYMIUM (1064 nm) LASERS

A symposium on "Research in Light Coagulation" sponsored by The Departments of Biophysics and Ophthalmology was held at the Medical College of Virginia in March 1963. Dr. Ham presented a paper on " Optical Masers (Lasers)".[9] Following an historical introduction of the development of lasers, the basic principles of ruby laser action were described in some detail. A ruby laser optical system designed to produce retinal lesions variable in size and severity was produced in the laboratory. A laser head was designed to contain a ruby rod 2 inches long and 0.25 inches in diameter which was pumped by 4 EG&G low pressure xenon lamps placed parallel to the rod axis and angularly spaced at 90° to each other around the periphery. Aluminum foil was wrapped around the lamps enclosing the ruby rod. Energy output per pulse was measured with a sensitive cone radiometer designed in this laboratory. The calibration constant was 0.0151 Joules per microvolt; one microvolt produced a deflection of four inches on a strip chart recorder. The ruby output was 0.062 Joules per pulse; laser action began 200 microseconds after the pumping light began and lasted for approximately 400 microseconds. Later cone radiometer designs increased the sensitivity to 0.00167 Joules per microvolt.

In a later design[10] the laser head contained a ruby rod (3"x$^1/_4$") with end faces optically flat but uncoated. A Nd glass rod could be substituted for the ruby rod. Pumping was accomplished by 8 EG&G FX-100 xenon lamps, connected separately into 2 sets of 4 lamps in series, each set separately but simultaneously discharged by a high voltage trigger, a cylindrical aluminum reflector surrounded the entire assembly. Provisions for both normal lasing and Q-switched operation were included in the laser head. Q-switching was accomplished by rotating a totally internal reflecting (TIR) prism at 13,200 rpm; an optically flat dielectric reflector (either 95 or 60% reflectivity) was used to complete the optical path of total length 19 cm. A complete optical system including the laser head was mounted rigidly on a maneuverable optical bench with 5° of freedom (3 translational, 2 rotational), thus providing a flexible system for irradiating the eye, a modified ophthalmoscope being used to reflect the beam into the eye. At a later stage in the research program the rotating TIR prism was replaced by a Kerr cell for Q-switching. The rabbit retina was exposed to laser pulses ranging from 400 to 200 microseconds and to Q-switched pulses of 30 nanoseconds (ns). The electronically pulsed xenon light source[7] provided white light pulses ranging from 175 microseconds to milliseconds and steady state cw exposures ranging from milliseconds to minutes.

There was a fundamental difference in the physical phenomena and biological consequences accompanying exposure of the mammalian retina to high power density (megawatts per cm^{-2} Q switched lasers) as compared to moderate power densities (kilowatts per cm^{-2} normal lasing pulses and xenon light pulses). Approximately 70 $mJ \cdot cm^{-2}$ from a 30 ns Q-switched laser pulse produced irreversible damage to the rabbit retina whereas it required 850 $mJ \cdot cm^{-2}$ to produce ophthalmoscopic visible damage from a 200 microsecond laser pulse. Moreover, the biological type of damage was different as evidenced by histological analysis.[8,11] In mild lesions induced in the rabbit retina by Q-switched ruby pulses the damage was confined to the retinal pigment epithelium (RPE) and the inner layers of the neural retina (2 to 5 $MW \cdot cm^{-2}$ delivered in 30 ns); at higher power densities (20 to 50 $MW \cdot cm^{-2}$) material was extruded into the outer retina and the vitreous. At these power density levels hemorrhaging into the vitreous occured; this was a catastrophic event that could result in loss of the eye. These observations suggested shock waves as the mode of biological damage to the retina. It is interesting to note that 25 years later, Q-switched and picosecond pulses of Nd:YAG laser radiation are being employed routinely in clinical practice to produce openings in the lens capsule after cataract extractions.

5. THRESHOLD RETINAL DAMAGE IN HUMAN VOLUNTEERS

Rabbits and monkeys were the animals of choice to determine retinal threshold damage from exposure to radiation sources like the sun, nuclear fireballs, xenon lamps, lasers and other optical sources. The demand for a realistic evaluation of the retinal hazard from nuclear weapons and the growing hazard from laser sources had accentuated the need for an accurate extrapolation of animal data to humans. Here we report on patients who volunteered to undergo light exposure either during phototherapy for diabetic retinopathy or before enucleation of the eye for malignant melanoma.

Our first volunteer, a white male age 51, was scheduled for enucleation of his right eye because of a diagnosis of malignant melanoma. Before and after exposures, he underwent a series of tests for visual acuity, visual fields and adaptometry. The optical source was the high intensity xenon lamp with associated optics as previously described.[7] A KG-3 filter removed wavelengths greater than 900 nm. Exposure times ranged from 130-140 ms, just below the human blink reflex estimated to be approximately 150 ms. Image size on the retina was about 1 mm in diameter. Spectral quality and exposure time grossly simulated exposures to a fireball from 10-20 KT nuclear weapons during the interval before the blink reflex interrupted the exposure. Radiant exposures required to inflict a mild lesion in the paramacular area ranged from 9.2-12.2 $J \cdot cm^{-2}$ and two exposures of 7.9 and 10.0 $J \cdot cm^{-2}$ did not produce visible lesions in the retinal periphery. A radiant exposure of 13.0 $J \cdot cm^{-2}$ covering the entire macula did not produce a visible lesion or permanently affect the visual acuity of this patient 15 hours after exposure. After macular exposure to 13 $J \cdot cm^{-2}$

he reported an after image "approximately the size of a goose egg" that lasted at least 5 hours but had disappeared the next morning (15 hours postexposure).

Another male volunteer who underwent similar exposures had a paramacular threshold ranging from 9.5 to 9.9 $J \cdot cm^{-2}$. However, exposure of the macula in this patient produced an absolute scotoma. In a third male volunteer the paramacular threshold was 9.7 $J \cdot cm^{-2}$. No exposure of the macula was possible in this patient because the fovea was detached. Two groups of diabetic retinopathy patients volunteered to undergo threshold exposures to the paramacula from the same optical source described above. These threshold exposures were extremely mild compared to those used in photocoagulating the peripheral retina for treatment of diabetic retinopathy. The paramacular threshold in one group of 18 white male patients was found to be 9.3 ± 1.56 $J \cdot cm^{-2}$; in the other group of black male patients the threshold was 7.9 ± 1.86 $J \cdot cm^{-2}$. In the following Table I[14], these data on human volunteers are compared with comparable data on monkeys and rabbits. The threshold for retinal injury in humans is significantly higher than that for monkeys and rabbits except for the ten black patients treated for diabetic retinopathy.

Table I Comparison of Retinal Burn Thresholds in Man, Monkey and Rabbit

	Area Exposed		
Species	Paramacula	Fovea	Comments
Man(A.E.B.)	9.0-12.2	13.0	Only temporary afterimage
Man(M.Y.)	9.5-9.9	9.7	Absolute central scotoma
Man(M.V.)	9.7		Foveal detachment
Man(White)	9.3 ±1.56		18 patients
Man(black)	7.9 ±1.86		10 patients
Monkey	5.9 ±1.5	5.7 ±0.35	22 rhesus monkey eyes
Rabbit	4.1 ±0.4		100 rabbit eyes

Human volunteers and patients treated for diabetic retinopathy are compared to monkeys and rabbits under identical conditions of exposure, namely, retinal image diameter, 1 mm; exposure time, 135 ms; optical source, a filtered Osram lamp (XBO 2500) producing spectrum 400-800 nm. Energy density on retina given in $J \cdot cm^{-2}$.

6. EXPERIMENTS WITH THE He-Ne LASER (632.8 nm) ON THE MONKEY RETINA

The helium-neon (He-Ne) continuous wave (cw) laser is the most widely distributed and generally employed laser in modern technology. Of the 18,000 lasers estimated (1970) to be in use, 11,150 or 62% were He-Ne lasers; these statistics did not include those used in the military services and the other governmental agencies. This research was undertaken to determine the He-Ne burn threshold in the retina of the mammalian eye.[12] The rhesus monkey was selected as the experimental animal of choice because of past experience with this species and

because simians in general represent a reasonably close approach to the visual processes in man; particularly, these animals have color vision and a well defined foveal and macular area with fairly uniform pigmentation of the fundus. It was recognized that minimal thermal damage was a gross approximation to retinal tissue damage. Nevertheless, minimal changes as observed with the ophthalmoscope should provide valuable data for setting safety standards. Other experiments in our laboratory had shown that rhesus monkeys exposed to radiant exposures 20% below the burn threshold did not exhibit a visual loss as determined by the Landolt ring testing system.[13]

The He-Ne laser source was a Spectra-Physics model 125 laser capable of emitting 80 mW of power. It was mounted on a maneuverable optical bench with 5 degrees of freedom so that the ophthalmologist using a modified ophthalmoscope fixed to the bench could direct the laser beam into the eye of the anesthetized monkey with pupils dilated to 8 mm or more. Results were given in terms of the mean corneal power in mW required to produce a threshold thermal lesion for image diameters on the retina of 50,116,298 and 460 micrometers and exposure times ranging from 20 ms to 10 s. Most importantly, the data predicted that for worst case accidental exposures to He-Ne lasers (whole beam without optics entering the eye) the threshold corneal power for irreversible damage to the monkey retina was about 7 mW. It was concluded that most available data indicated that the human retina was less suseptible to thermal damage than the monkey or the rabbit. It was recommended that the total He-Ne power entering the human eye be limited to one mW or less.

7. EVALUATION OF THRESHOLD DATA FOR RETINAL DAMAGE IN THE RHESUS MONKEY IN TERMS OF VISUAL ACUITY AS TESTED BY THE LANDOLT RING SYSTEM[13]

The rhesus monkey was chosen for these experiments because it had been demonstrated that these animals could be trained to perform tasks requiring a high degree of visual acuity and because extensive data on threshold damage to the rhesus retina had been collected by a number of different investigators. Monkeys trained and tested at Holloman Air Force Base for visual acuity by the Landolt ring technique were flown to Richmond, VA for exposure to known amounts of radiation emitted by the experimental xenon lamp coagulator previously described.[7] The spectral distribution of this optical source was made to simulate grossly the radiation spectrum of a nuclear fireball within the earth's atmosphere. An exposure time of 135 ms was chosen as typical of the radiant exposure delivered by a 10-20 KT weapon. The objective was to evaluate permanent visual decrement in terms of radiant exposure to the retina.

In these experiments the image diameter on the retina was calculated individually for each animal by multiplying the focal length (distance from posterior surface of the lens to the retina as measured separately for each monkey by echo or sonograms) by the divergence in

radians of the light beam incident on the cornea. This divergene was set accurately at 4.5° so that the image diameter on the retina was approximately 1 mm, an area large enough to cover most of the macula area in the rhesus monkey. The procedure was to determine threshold damage in the paramacula of each eye by means of a series of exposures (usually 5) which could be used to define the threshold by interpolation. The threshold was defined as the appearance of a just discernible lesion as seen with the ophthalmoscope, 5 minutes postexposure. Each exposure was monitored for total energy entering the dilated pupil (> 8 mm) of the anesthetized animal by means of a beam splitter that reflected a small portion of the light to a fast photodiode which had been previously calibrated against a cone radiometer placed in the position occupied by the eye. Once having determined the paramacular threshold in the eye, the entire macular area was exposed to either 100, 80 or 50% of the threshold radiant exposure.

In this study 14 animals (28 eyes) were used; two animals (4 eyes) served as controls. The average acuity before exposure, measured in minutes of arc for 28 eyes, was 0.79 ± 0.07 which corresponds to a visual acuity between 20/15 and 20/20 in the rhesus monkey. The mean paramacular threshold for 37 eyes as defined by the 5 minute postexposure criteria was 6.67 ± 1.06 J·cm^{-2}. Since each monkey was exposed also to 100, 80, or 50% of the thrshold radiant exposure, there resulted a wide range of macular exposures ranging from 2.7 to 10.7 J·cm^{-2}. Visual decrement was defined in this study as the difference in visual acuity before and after exposure of the macula, divided by the visual acuity before exposure of the macula. There was no significant difference in decrement between control eyes and those eyes exposed up to and including 5 J·cm^{-2}. This suggested that the control and exposed eyes be divided into two groups: controls plus those exposed to less than 5 J·cm^{-2}, and those eyes exposed to greater than 5 J·cm^{-2}. The difference in visual decrement between these two groups was significant ($P<0.005$).

There is some evidence that exposures greater than 5 J·cm^{-2} do not result necessarily in a permanent loss of visual acuity. In one group of 12 eyes the average macular exposure was 6.2 J·cm^{-2}. This caused a significant visual decrement at 2 days postexposure but at 12 days postexposure there was recovery to preexposure levels; from this time on, there was no significant difference between control and exposed eyes. In the other group of 12 eyes exposed to 7.1 ± 0.63 J·cm^{-2} there was a highly significant loss in visual decrement that persisted and even dropped further during the 8 days of postexposure testing. There were no significant differences in macular thresholds as compared with paramacular thresholds. No macular exposure of 5 J·cm^{-2} or less produced an observable macular lesion, whereas the paramacular threshold for 24 eyes was 6.67 ± 1.06 J·cm^{-2}.

It was concluded from this study that visual acuity in the rhesus

monkey as judged by a monocular presentation of Landolt test rings was related closely to threshold retinal damage as determined in the paramacular by observation with the ophthalmoscope at 5 minutes postexposure. There was significant loss of monocular visual acuity at the P less than 0.05 level for rhesus monkeys who received a radiant exposure greater than 5 $J \cdot cm^{-2}$ in the macular area of the retina

8. EARLY STUDIES ON SOLAR RADIATION AS A RETINAL HAZARD

The sun makes life possible on this planet but solar radiation is also a hazard to the manmmalian eye, particularly the retina. Eclipse blindness was known to the ancients. It still constitutes a hazard to modern man whenever a solar eclipse occurs. In the early seventies we undertook an investigation on the ocular hazard of viewing the sun at the top of the atmosphere (high flying aircraft, space exploration) and at sea level.[14] Since reliable data on thresholds for solar retinitis were not available it was necessary to simulate the solar spectrum in the laboratory in order to obtain threshold data in an experimental animal that hopefully could be extrapolated to man. We chose the rhesus monkey for reasons already stated in this report.

The sun subtends an angle of 32 minutes of arc (9.31 milliradians) at a distance of one astronomical unit, producing an image diameter of 158 micrometers on the human retina. The solar spectra at the top of the atmosphere and at sea level were taken from the Handbook of Geophysics and Space Environments. The source used to simulate these spectra was a xenon high pressure lamp (Osram XBO 2500 W) filtered by an Aerospace Control Corporation filter (7187). A comparison of our simulated solar spectra with those of the sun showed that our optical source was somewhat deficient below 400 nm and in the near infrared but nonetheless a reasonable approximation of the solar radiation over the spectral range 400-1400 nm. Power input to the eye exceeded that of the sun for pupillary diameters less than 8 mm.

Transmittances through the ocular media of man and monkey as measured in our laboratory (see Fig. 2, ref.14) were used to calculate retinal irradiances. The solar constant at zenith, unattenuated by the atmosphere was taken as 102 $mW \cdot cm^{-2}$ for the spectral range 400-1400 nm and 64 $mW \cdot cm^{-2}$ at sea level. The integrated transmittance of the human ocular media for this spectral band was 0.735 at the top of the atmosphere and 0.781 at sea level. Retinal irradiances on the basis of an image diameter of 158 micrometers were calculated for pupillary diameters ranging from 1.5 to 8 mm and are shown in Table II.

Table II. Retinal Irradiance ($W \cdot cm^{-2}$) vs Pupillary Diameter (mm)

Pupillary Diameter (mm)	Retinal Irradiance ($W \cdot cm^{-2}$) Top of Atmosphere	Sea Level
1.5	6.76	4.51
2.0	12.0	8.01
3.0	27.0	18.0
4.0	48.0	32.0
5.0	75.1	50.0
6.0	108.0	72.1
7.0	147.0	98.1
8.0	192.0	128.0

The optical assembly used to expose the monkey retina to the simulated solar spectrum was basically similar to the Zeiss photocoagulator except for a more powerful quartz condenser lens and the use of a Zeiss fundus camera to view and photograph the retina before, during and after exposure. Corneal irradiance was controlled by an adjustable diaphragm without change in spectral quality and the divergence of the beam at the cornea was adjusted to produce a spot size of 138 micrometers on the monkey retina. Animals were anesthetized with sodium pentobarbital, dilated with cyclopentolate hydrochloride and phenylephrine hydrochloride and firmly bound to a sterotaxic platform device with six degrees of freedom so that the beam of radiation could be placed at any desired location on the fundus. A lid speculum kept the eye open during exposures, while physiological saline was applied frequently to prevent drying of the cornea.

Preselected exposure times were made with an electronic timer that controlled an air operated shutter. The experimental procedure following the appearance of a mild retinal lesion immediately after exposure was to reduce the irradiance in small steps (5-10%) until no lesion was discernible with the fundus camera; at least two additional exposures were delivered at irradiances below this level. A fundus photograph was taken before returning the animal to his cage. Twenty-four hours later the monkey was anesthetized again and examined with the fundus camera. The faintest discernible lesion was taken as threshold injury. There were always one or two more exposures that did not appear at 24 hours postexposure. This interpolation technique required between 5 and 7 exposures to define the threshold radiant exposure and the total number of exposures per monkey eye ranged between 25 and 30. Each exposure was monitored by means of a beam splitter reflecting into a photodiode calibrated previously against a cone radiometer placed at the site of the eye. The threshold data on 5 monkeys (10 eyes) were obtained at preselected exposure times of 1,10,30,60 and 180 seconds. Results are given in Table III where each

data point represents the mean and standard deviation for 10 thresholds in 10 monkey eyes. Estimates of maximum temperature at the center of the lesion were calculated from the paper by White, Mainster et al[15] on chorioretinal temperature increases from solar observation which predict a 1°C rise above ambient for an irradiance on the retina of 6.77 $W \cdot cm^{-2}$.

Table III

Power entering the eye or corresponding retinal irradiance required to produce a threshold lesion in the rhesus retina for various exposure times to a simulated solar spectrum at sea level.*

Exposure time s	Power entering eye mW	Retinal Irradiance $W \cdot cm^{-2}$	Maximum Temperature °C
1	33.2 ±3.7	131.0 ±14.5	19.4
10	21.4 ±2.2	84.1 ± 8.6	12.4
30	14.6 ±3.1	57.4 ±12.2	8.5
60	8.4 ±1.7	33.0 ± 6.7	4.9
180	4.8 ±0.8	18.9 ± 3.2	2.8

*Image diameter on retina 158 micrometers; simulated solar spectrum 400-1400 nm; integrated transmittance through monkey ocular media 0.770.

An interesting feature of the data in Table III was that for exposure times of 60 seconds or greater the maximum temperature at the RPE-photoreceptor interface was less than 5°C above ambient, a temperature rise too low to produce thermal denaturation to tissue. This suggested that thermally enhanced photochemical effects were responsible for the observed retinal lesion. The results shown in Tables II and III are combined in Figure 1 which are plots of retinal irradiance in $W \cdot cm^{-2}$ vs pupillary diameter in mm for a human viewing the sun at the top of the atmosphere and at sea level. Superimposed on these curves are the threshold data from Table III. These data are represented by straight lines parallel to the x-axis at the retinal irradiances corresponding to exposure times of 1,10,30,60 and 180 seconds. The intersection of these lines with the curves gives the pupillary diameter required to provide the necessary irradiance for a retinal threshold lesion at a given exposure time. The temperature corresponding to a given retinal irradiance is plotted on the y-axis to the right. For example, to produce a threshold lesion in the monkey retina in 180 seconds at sea level would require a pupillary diameter of 3.1 mm and the maximum retinal temperature would be 2.8°C above ambient. At sea level an exposure time of 1 second would require a pupillary diameter greater than 8 mm to produce a threshold lesion in the monkey. Threshold lesions inflicted in exposure times less than 30 seconds produce temperature rises of approximately 10°C or greater and represent thermal injury or so-called retinal burns but for exposure

times greater than 30 seconds the lesion is primarily photochemical in nature.

Most filters used in sunglasses transmit a large part of the infrared in the solar spectrum at sea level between the wavelengths 700-1400 nm. To explore the relative toxicity to wavelengths between 400-1400 nm vs 700-1400 nm, 7 monkey eyes were exposed to the xenon source transmitted through a Jena glass RG-715 (RG 10) filter under conditions similar to those employed in determining the threshold data listed in Table III, namely image diameter on the retina of 158 micrometers, simulated solar spectrum 700-1400 nm and integrated transmittance through the monkey ocular media 0.707. The results are listed in Table IV where power entering cornea in mW, retinal irradiance in $W \cdot cm^{-2}$, and estimated maximum temperature in °C above ambient are given for exposure times of 10, 30, 60 and 180 seconds. There was insufficient power in our optical source to produce a retinal lesion in 1 second.

Figure 1 Retinal Irradiance ($W.cm^{-2}$) vs Pupillary Diameter(mm)
At Sea Level (---X--) and at the Top of the Atmosphere (—0—).

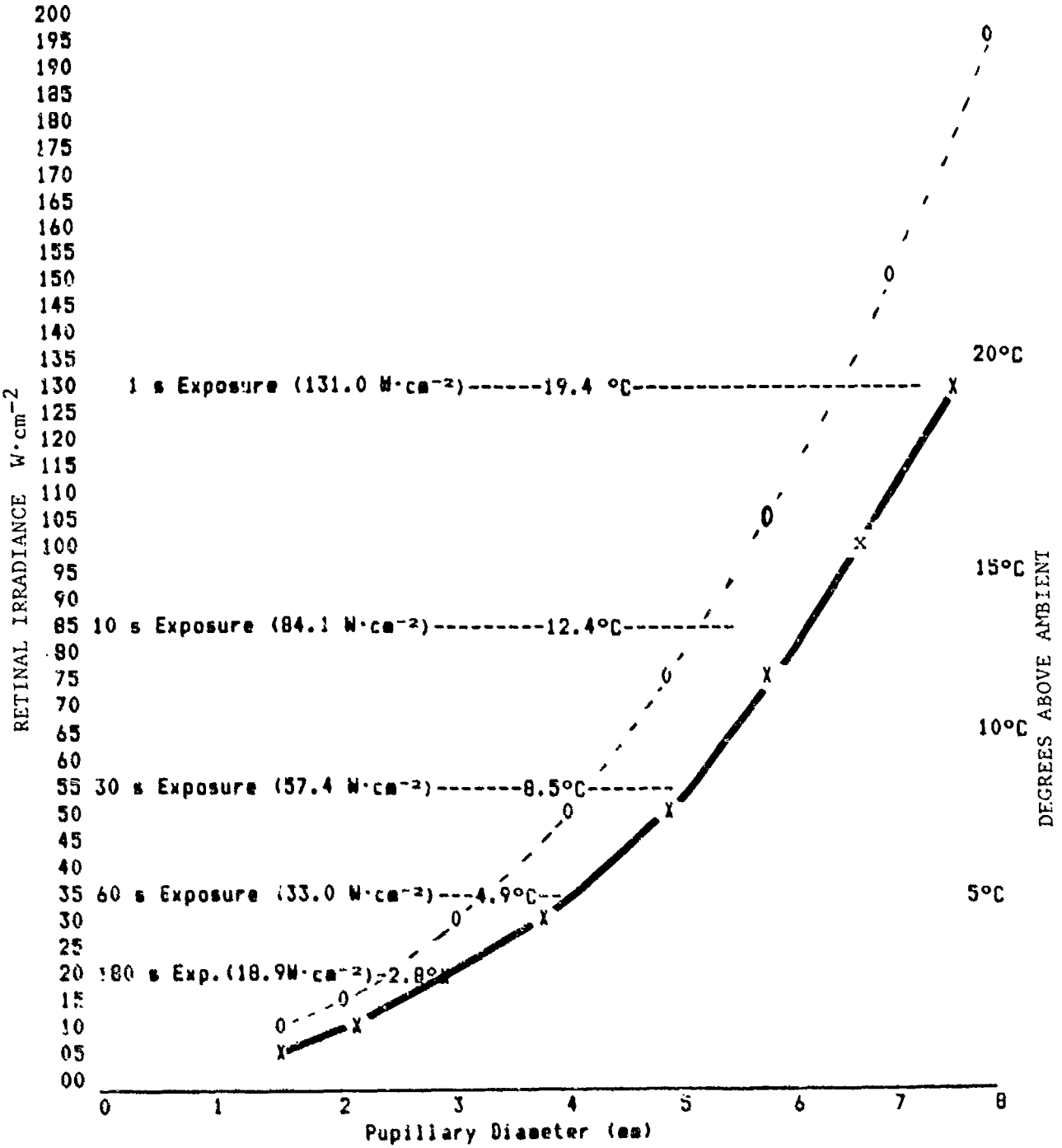

Table IV

Power entering the eye or corresponding retinal irradiance required to produce a threshold lesion in the rhesus retina for various exposure times to a simulated solar spectrum from 700-1400 nm*.

Exposure time s	Power entering eye mW	Retinal irradiance $W \cdot cm^{-2}$	Max. temperature °C
10	43.3 ±5.8	156 ± 20.9	23.0
30	37.0 ±7.0	133 ± 25.2	19.7
60	32.0 ±7.7	115 ± 27.8	17.0
180	27.0 ±4.2	97.4± 15.1	14.4

*Retinal image diameter 158 micrometers; retinal spectral distribution 700-1400 nm; integrated transmittance 0.707; each data point represents the mean and std. deviation from 7 monkey eyes.

A comparison of the thresholds listed in Table IV for the infrared spectrum 700-1400 nm with the thresholds listed in Table III for the spectrum 400-1400 nm shows that the toxicity of the full spectrum containing the visible wavelengths is much greater than that of the infrared spectrum, ranging from a factor of 2 for 10 second exposures to 5 for 180 second exposures. A comparison of maximum retinal temperatures provides strong evidence that lesions produced by the infrared spectrum 700-1400 nm are thermal in nature since even for a 3 minute exposure the temperature was 14.4°C above ambient. On the other hand the spectrum containing visible light 400-1400 nm induced temperatures below 10°C for exposures of 30 second duration or longer. From these data it could be inferred that the longer wavelengths (> 700 nm) produced thermal injury or retinal burns whereas the shorter wavelengths 400-700 nm produced a type or types of photochemical or actinic damage supplemented by thermal enhancement. This led to the belief that the short wavelengths in the solar spectrum were primarily responsible for solar retinitis and the infrared radiation produced injury only when the power level was high enough to cause a retinal burn. In a later and more elaborate study with a simulated solar source we proved definitively that in the rhesus monkey solar retinitis and eclipse blindness were photchemical phenomena caused by the short wavelengths in the solar spectrum and that the infrared component produced negligible injury[16].

9.RETINAL LIGHT TOXICITY AS A FUNCTION OF WAVELENGTH.

The observations noted above in Section 6 prompted us to make a definitive study of photic damage to the retina as a function of wavelength.[17]

We exposed the rhesus retina to 8 monochromatic laser lines extending from 441 nm in the blue visible to 1064 nm in the near infrared. We

found that the retinal sensitivity increased dramatically in the blue region of the spectrum, especially for long exposure times (1000 s). The corneal power required to produce a minimal lesion in 1000 s increased by three orders of magnitude in going from 441 nm to 1064 nm. Furthermore, the type of lesion produced by 441 nm was entirely different from that produced by 1064 nm. The latter was a retinal burn whose image diameter was smaller than the exposed site and at a temperature rise of 23°C, whereas the 441 nm lesion occured with negligble temperature rise (< 0.1°C) and the lesion appeared two days after exposure and was full size. This was clear evidence that some type or types of actinic or photochemical reaction(s) were produced by short wavelength light.

Histologically as well as morphologically, minimal burn lesions differ markedly from minimal blue light lesions.[17] When thermal lesions are examined by light microscopy at 24 to 48 hours postexposure it is found that many of the photoreceptor cells have been irreversibly damaged (pyknotic) as well as the cellular structure of the retinal pigment epithelium (RPE). Destruction is greatest at the center of the lesion, tapering off toward the periphery because maximum temperature occurs at the center of the irradiated area. Thus, a minimal burn lesion is always smaller than the irradiated area. In contrast, minimal blue light (441 nm) lesions are nearly uniform across the irradiated area and do not appear until 48 hours after exposure. Histologically, damage appears initially in the RPE at 48 hours postexposure. The RPE is inflammed and edematous, melanin pigment granules are agglutinated resulting in depigmentation, and macrophages filled with melanin granules appear in the subretinal space.[18] The photoreceptors do not begin to show major damage until 5-6 days postexposure. By 20 to 30 days postexposure a minimal blue light lesion has healed leaving only hypopigmentation and macrophages in the subretinal space. Tests with rhesus monkeys trained to perform a visual task show that 20/20 vision is lost 5-6 days postexposure but returns in 20-30 days.[19] After 60 days the macrophages have disappeared from the subretinal space; at 90 days a slight granular and depigmented area remains in the RPE that bears a suggestive resemblance to age-related macular degeneration (AMD).

We had extended our investigation of retinal sensitivity to radiation into the near ultraviolet (UV). Aphakic monkeys (lens removed surgically from one eye) were exposed to 405, 380, 350 and 325 nm radiation from our 2500 W xenon lamp system with quartz optics. We found that the rhesus retina was 6 times more sensitive to wavelengths 350 and 325 nm than to 440 nm blue light.[20] The photochemical effects of near UV radiation are similar but more exaggerated than those of blue light damage and include, in addition to injury to the RPE cells, extensive damage to the photoreceptors, especially the cones.

10. OCULAR HAZARD FROM EXPOSURE TO NANOSECOND AND PICOSECOND PULSES OF LASER RADIATION (Nd:YAG 1064 AND 532 nm AND CO_2 10.6 μm AND HF

2,5-3,0 μm).

These experiments were supported by H and L Divisions, Los Alamos Scientific Laboratory (LASL) as well as by Army Contract DADA 17-721-C-2177. The actual exposures were performed during a series of visits to LASL between 1974 and 1976. In February 1972 LASL created a new technical division, L-Division (Laser Research and Technology), to explore the feasibility of utilizing laser radiation to produce thermonuclear fusion. Among the techniques selected for exploration were mode-locked Nd:YAG lasers producing nanosecond pulses. Concern for the potential ocular hazards from such laser pulses was the motivation for the research reported here.

For picosecond pulses of mode-locked Nd:YAG 1064 nm radiation or it first harmonic 532 nm, the mammalian retina is the tissue at risk because of the transmission characteristics of the mammalian ocular media; accordingly the rhesus monkey was selected as the experimental animal of choice. In the first series of experiments, 7 rhesus monkeys (14 eyes) were exposed to 1064 nm radiation in single pulses of 25 to 35 picoseconds.[21,22] Threshold injury resulted from single pulses with a mean energy of 13 ±3 microjoules at the cornea. Electron microscopy of the retina revealed that damage was highly localized in the photoreceptor and pigmented epithelial cells of the outer retina. Membrane disruption, distorted outer segments and abnormal melanin granules resembling fetal premelanosomes were observed. An unintentional (accidental) exposure of 282 microjoules at the cornea produced a massive hemorrhage into the vitreous. Another exposure of 150 microjoules caused a subretinal hemorrahage. Analysis of the damage suggested that the melanin granules were raised transiently to very high temperatures resulting in the production of acoustic and shock waves within the retina.

In a second series of experiments both Nd:YAG 1064 nm pulses and the first harmonic, Nd:YAG 532 nm pulses, were used to determine threshold damage.[23] Ten rhesus monkeys were exposed to single picosecond pulses (25-35 ps) from the unfoscused beam producing spot diameters on the retina of approximately 25 micrometers, as well as single pulses at 1064 nm from focused beams that produced 430, 630 and 725 micrometer spot diameters on the retina. Ocular damage thresholds for the unfocused beam entering the eye were 8.7 ±4.8 microjoules at 1064 nm and 18.2 ±8.3 microjoules at 532 nm. Thresholds for the focused 1064 nm pulses at spot diameters of 430, 630 and 725 micrometers were 1521 ±330, 1017 ±700 and 1184 ±334 microjoules respectively, corresponding to radiant exposures on the retina of 1.6, 0.50 and 0.44 $J \cdot cm^{-2}$. Ultrastructual analysis indicated that at 1064 nm the damage mechanism(s) were independent of image size on the retina. Damage was postulated to result from shock waves produced by transient heating of melanin granules. At 532 nm, additional damage to the outer segments of the photoreceptors was interpreted as photochemical damage from light absorption by the visual pigments (rhodopsin + the cone pigments) superimposed upon mechanical shock damage to both the

retinal pigment epithelium and the immediately adjacent portions of the outer segments.

In another and final series of experiments[24] the ocular effects of single pulses of 10.6 micrometer and 2.5-3.0 micrometer Q-switched laser radiation were investigated. Since radiation of these wavelengths is completely absorbed by the cornea, the rabbit was selected as the experimental animal of choice. The CO_2 laser used in the first set of experiments had the capability of providing single pulses of 1.4 ns duration with sufficient energy per pulse to cause severe damage to the rabbit cornea. The diameter of the laser beam at the site of exposure was about 2 cm in diameter with a beam profile which was only approximately Gaussian. To remedy this, a diaphragm 0.95 cm in diameter was inserted in the beam to provide a more uniform distribution of power density. The rabbit cornea was placed immediately behind the diaphragm. A beam splitter reflected a small portion of each pulse into a detector (Scientech Joulemeter) which had been calibrated against another Scientech Joulemeter placed at the position of the eye. In this manner each pulse of energy could be monitored and recorded.

A total of 15 chinchilla rabbits (30 eyes) were exposed to single pulses. Animals were examined immediately after exposure using fluorescein to enhance contrast when viewing with the biomicroscope (slit lamp). Examinations were repeated at 24 and 48 hours postexposure. After euthanasia eyes were enucleated for histological examination. Animals exposed to 5-6 $mJ \cdot cm^{-2}$ developed a slight stippling of the cornea at 48 hours postexposure. No stippling was visible prior to 48 hours after exposure. This damage was extremely superficial and completely reparative within 72 hours postexposure. Histological examination revealed a swollen surface with disturbance of wing cells, probably caused by edema. This type of damage was designated arbitrarily as threshold in nature and was completely reparative within 72 hours postexposure. Exposures to 13-15 $mJ \cdot cm^{-2}$ developed a slight opacity either immediately or within 24 hours postexposure. Visible damage consisted of stippling with irregular outlines of the radiation beam and progressive graying within 48 hours postexposure. Histological examination disclosed a swollen epithelium with slight disorientation of the basal cell layer; longitudinal alignment of these cells was impaired and wing cells were swollen. Damage was still minor with complete recovery with 72 hours postexposure. At radiant eposures of 20-30 $mJ \cdot cm^{-2}$ damage was immediately apparent with the appearance of some vacuoles in the epithelial layers. Histologically, all layers of epithelial cells showed some disruption. Damage at this level may not be entirely reparable.

om the standpoint of establishing safety levels for personnel around installations producing nanosecond pulses of CO_2 radiation, these experiments indicated that radiant exposures slightly above 5 $mJ \cdot cm^{-2}$

produced very mild but reparable damage to the rabbit cornea. This corresponds to an irradiance of about 3.6 $MW \cdot cm^{-2}$. The half-value layer for absorbtion at this wavelength is about 10 micrometers of water. Even the tear layer would provide apprecible protection. From the histology it can be inferred that nearly all of the energy is absorbed within the 5 layers of epithelial cells of the cornea. The basic mechanism producing damage is thought to be severe sonic transients producing mechanical damage (shear forces). The remarkable reparative powers of corneal tissue are such as to minimize the biological effects of a mild corneal exposure.

Under normal operating conditions the hydrogen fluoride (HF) laser tested at Los Alamos for ocular effects emitted single pulses of 100 ns duration containing 11 monochromatic lines ranging in wavelength from 2.5-3.0 micrometers. This laser was also capable of emitting a 4 ns pulse superimposed on the 100 ns pulse; a major portion of the energy was emitted within the 4 ns pulse, with a tail extending out to 100 ns. The rabbit cornea was exposed to both types of pulses and also to a single monochromatic line at 2.9 micrometers of 100 ns duration. Methods of exposure, screening and postexposure assay were similar to those descibed for the CO_2 laser.

A total of 8 rabbits (16 eyes) were exposed to the 4 ns pulse superimposed on the 100 ns pulse. Radiant exposures ranging from 4.3-6.8 $mJ \cdot cm^{-2}$ produced superficial damage to the cornea. Stippling was immediately visible and was still visible at 6 days postexposure. There was no follow-up beyond 7 days but it seems certain that damage at this level was fully reparable. Histological examination at 6 days postexposure showed no damage beyond the wing cells; they were slightly enlarged and swollen. No fractionation of epithelial cell layers similar to that seen at higher levels of exposure was noted. In the range 14-20 $mJ \cdot cm^{-2}$ corneal damage was mild and probably reparable with time. Usually, a light gray area was visible at 6 days, representing a partial profile of the laser beam. Histological examination disclosed fractionation of the epithelial cell layers down to the basal layer. There was some evidence of shock wave effects immediately after exposure,i.e. a slight depression of the cornea in the impact area. At these levels complete recovery with time can be assumed. The stromal layer of the cornea was intact in all sections examined histologically, even for radiant exposures as high as 78 $mJ \cdot cm^{-2}$. At HF wavelengths (2.5-3.0 micrometers) the half-value layer for absorption in water is considerably less than 10 micrometers. Vaporization of the tear layer probably helps protect the cornea.

A total of 8 rabbits (16 eyes) were exposed to single (2.9 micrometer) wavelength pulses of 100 ns duration and 4 animals (8 eyes) were exposed to 100 ns pulses containing 11 wavelengths ranging from 2.5-3.0 micrometers. There were no outstanding biological differences between the 100 ns + 4 ns, 100 ns (2.9 micrometers) and 100 ns (2.5-3.0 micrometers) pulses. The HF laser effects on the rabbit

cornea were very similar to those caused by exposure to the CO_2 laser. The energy from the CO_2 and HF lasers is completly absorbed in the superficial layers of the cornea, creating a sharp sonic or shock wave which can disrupt the epithelial cells but does not penetrate to the stroma, at least for levels of exposure used in these studies. If damage does not penetrate to the stroma the remarkable recuperative powers of the cornea are able to repair the injury.

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13. ABBREVIATIONS AND SYMBOLS IN THIS WORK

AMD	: age-related macular degeneration
mm	: millimeter
nm	: nanometer
s	: second
ms	: millisecond
ns	: nanosecond
ps	: picosecond
PRF	: pulse repetition frequency
RPE	: retinal pigment epithelium
Hz	: Hertz
He	: helium
Ne	: neon
Ar	: argon
Kr	: krypton
Ga	: gallium
As	: arsenide
ND	: neodymium
YAG	: yttrium aluminum garnet
HF	: hydrogen fluoride
DF	: deuterium fluoride
CO_2	: carbon dioxide
CD	: cadmium
EG&G	: Edgerton, Germeshausen & Grier
MW	: Megawatt
kW	: Kilowatt
W	: Watt
mW	: milliwatt
uW	: microwatt
KT	: kiloton
J	: Joule
mJ	: millijoule
µJ	: microjoule

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